Cancer Drugs Fund

Managed Access Agreement

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia [TA663]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia in people without del(17p)/TP53 mutation and for whom FCR and BR are suitable [TA663]

Company name: AbbVie Ltd

Primary source of data collection: CLL13 on-going clinical study

Secondary source of data collection: Public Health England routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set

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Public Health England Agreement Manager	Rebecca Smittenaar, Analytical Lead
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1 Purpose of data collection arrangement

1.1 The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia in people without del(17p)/TP53 mutation and for whom FCR and BR are suitable [TA663]**.** A positive recommendation within the context of a managed access agreement (MAA) has been decided by the appraisal committee for the subgroup specified.

2 Commencement and period of agreement

2.1 This data collection arrangement shall take effect on publication of the managed access agreement.

2.2 Estimated dates for data collection, reporting and submission for CDF guidance review are:

End of data collection (primary source)	Primary study completion is expected January 2023
Data available for development of company submission	Clinical study report is expected in Q4 2023
Anticipated company submission to NICE for guidance review	June 2024

2.3 AbbVie anticipates the results from the additional data collected during the Cancer Drugs Fund period will be incorporated into an evidence submission and the updated economic model by June 2024.

2.4 AbbVie acknowledges their responsibility to adhere as closely as possible to the timelines presented in the document.

2.5 The review of this guidance, at the end of the managed access period, will be conducted as a full technology appraisal and Abbvie will be required to pay the charges associated with this process. A full technology appraisal will be required to allow data from the CLL13 trial and real-world data collection to be incorporated into the economic model and to ensure sufficient time and resource are allocated to review this new evidence.

2.6 NICE will, as far as is practicable, develop the scope and schedule the review into the technology appraisal work programme to align with the estimated dates for the end of data collection. The guidance review will use the process and methods in place at the time the invitation to participate is issued. For further details of the expected timelines for a single technology appraisal guidance review see the technology appraisal process guide.

2.7 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the end of data collection and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the guidance review timelines described in NICE's guide to the processes of technology appraisal.

2.8 The company is responsible for paying all associated charges for a review. Further information is available on the NICE website.

2.9 The company must inform NICE and NHS England and NHS Improvement of any anticipated changes to the estimated dates for data collection at the earliest opportunity.

2.10 Any changes to the terms or duration of any part of the data collection arrangement must be approved by NICE and NHS England and NHS Improvement.

2.11 If data collection is anticipated to conclude earlier than the estimated dates for data collection, for example due to earlier than anticipated reporting of an ongoing clinical trial, the company should note:

- Where capacity allows, NICE will explore options to reschedule the guidance review date to align with the earlier reporting timelines.

- It may be necessary to amend the content of the final SACT or real-world data report (for example if planned outputs will no longer provide meaningful data).

2.12 If data collection is anticipated to conclude later than the estimated dates for data collection, the company should note:

- The company must submit a written request to NICE and NHS England and NHS Improvement, with details of the extension requested, including an explanation of the factors contributing to the request.
- It may be necessary for the company to mitigate the impact of any delay, and reduce any risks of further delays.
- In the event of an extension, it may not be possible to amend the date of the final SACT or real-world data report, although NICE will explore options with Public Health England to provide data over the extended period.

2.13 NICE and NHS England and NHS Improvement may consider the data collection agreement no longer valid, and withdraw the technology from the Cancer Drugs Fund for the following, non-exhaustive, grounds:

- The primary sources of data are delayed, without reasonable justification.
- The primary sources of data are unlikely to report outcome data that could resolve the uncertainties identified by the technology appraisal committee.
- Amendments are made to the marketing authorisation.

3 Patient eligibility

3.1 Key patient eligibility criteria for the use of venetoclax in combination with obinutuzumab in the Cancer Drugs Fund include:

- application is made by for the initiation of systemic anti-cancer therapy with ventoclax in combination with obinutuzumab by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- patient has chronic lymphatic leukaemia (CLL) or small lymphocytic lymphoma (SLL)
- patient has been tested for 17p deletion and TP53 mutation and the results are negative
- patient has symptomatic disease which requires systemic therapy
- patient has not received any previous systemic therapy for CLL/SLL
- patient has a performance status of 0 or 1 or 2
- in the absence of this venetoclax plus obinutuzumab treatment option, the patient would otherwise have been treated with the combination of fludarabine, cyclophosphamide and rituximab (FCR) or the combination of bendamustine and rituximab (BR).
- venetoclax will be given in combination with obinutuzumab and that the venetoclax dose titration schedule will only be commenced after the patient has received the first 3 doses of obinutuzumab in cycle 1 (on days 1±2, 8 and 15) i.e. the venetoclax dose titration schedule is planned to commence on cycle 1 day 22 and be completed on cycle 2 day 28.
- patient has been prospectively assessed for the risk of the development of tumour lysis syndrome with venetoclax and that appropriate risk mitigation strategies have been put in place.

- patient has been assessed specifically for potential drug interactions with venetoclax.

- The maximum treatment duration of venetoclax in this indication is until day 28 of the 12th cycle of treatment (ie the maximum duration of venetoclax treatment is for 45 weeks, consisting of 1 week from cycle 1 day 22 followed by 11 cycles of 4-weekly cycles of venetoclax in cycles 2-12). The treatment duration of obinutuzumab is for a maximum of 6 cycles of obinutuzumab.

- venetoclax is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment or until the end of cycle 12 (as measured above), whichever of these events is the sooner.

- a formal medical review as to whether treatment with venetoclax in combination with obinutuzumab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.

- when a treatment break of more than 6 weeks beyond the expected 4-weekly cycle length is needed, a treatment break approval form will be completed to restart treatment, including as appropriate if the patient had an extended break on account of Covid-19.

- venetoclax and obinutuzumab will be otherwise used as set out in their respective Summary of Product Characteristics (SPCs).

3.2 The estimated patient numbers per year for this technology within the Cancer Drugs Fund are:

As estimated by the company	[redacted]

As estimated by NICE Resource Impact Assessment team	[redacted]

4 Area(s) of clinical uncertainty

4.1 The appraisal committee identified the following key areas of uncertainty during the course of the appraisal process:

1. Immaturity of the overall survival data,
2. relative effectiveness of the treatment compared to fludarabine, cyclophosphamide and rituximab (FCR), and bendamustine and rituximab (BR)

4.2 The committee concluded that further data collection within the Cancer Drugs Fund could resolve these uncertainties. For further details of the committee's discussion see section 3 of the Final Appraisal Document.

5 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	○ CLL13 trial (MO29596) NCT02950051
Secondary sources	○ Systemic Anti-Cancer Therapy (SACT) dataset ○ NHS England and NHS Improvement's Blueteq data

Description of sources

5.1 CLL13 (NCT02950051) is an ongoing trial sponsored by the German CLL Study Group. The aim of this study is to evaluate if standard chemoimmunotherapy (FCR, BR) in frontline treatment of physically fit CLL patients without del17p or *TP53* mutation can be replaced by combinations of targeted drugs (Venetoclax, Ibrutinib) with anti-CD20-antibodies (Rituximab, Obinutuzumab).

It is a phase 3 multicentre, randomized, prospective, open-label trial with four arms:

- Standard Chemoimmunotherapy (FCR/BR)
- Rituximab Plus Venetoclax (VenR)
- Obinutuzumab (GA101) Plus Venetoclax (VenO)
- Obinutuzumab Plus Ibrutinib Plus Venetoclax (VenIO)

The population of interest is obinutuzamb plus venetoclax (VenO) compared with standard chemoimmunotherapy (FCR/BR)

5.2 NHS England and NHS Improvement's Blueteq database captures the Cancer Drugs Fund population. NHS England and NHS Improvement shares Blueteq data with Public Health England for the Cancer Drugs Fund evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and NHS Improvement and Public Health England.

5.3 The Systemic Anti-Cancer Therapy (SACT) dataset, is a mandated dataset as part of the Health and Social Care Information Standards. Public Health England is responsible for the collection, collation, quality-assurance and analysis of this dataset.

5.4 Datasets collected and collated by Public Health England will collect data, including via the SACT dataset, alongside the primary source of data collection.

6 Outcome data

Clinical trial

6.1 The following outcomes will be collected in CLL13:

Co-primary endpoints

- Progression free survival (PFS) for the comparison of VenIO vs. standard chemoimmunotherapy (SCIT)
- Undetectable minimal residual disease (MRD) rates in peripheral blood (PB) at month 15 for the comparison of VenO vs. SCIT

Secondary endpoints

- PFS (all other comparisons, including the comparison of interest: standard chemoimmunotherapy vs. VenO)
- MRD rates in PB at month 15 (all other comparisons)
- Overall response rate (ORR)
- Rates of complete response (CR) or CR with incomplete recovery of the marrow (CRi)
- Event-free survival (EFS)
- Overall survival
- Duration of response
- Time to next CLL treatment
- Safety parameters:
    - Type, frequency, severity and relationship to study treatment of
        - adverse events (AEs) and
        - adverse events of special interest (AESI)
- Health-related quality of life (HrQoL) and compliance by MARS and EORTC QLQC30 and QLQ-CLL16 questionnaires

CLL13 will resolve the clinical uncertainty by providing direct evidence for the comparison of Venetoclax plus Obinutuzumab (VenO) with FCR and BR in people with CLL for whom FCR and BR is suitable. The trial will provide key outcomes for the economic model such as PFS, OS and safety data.

Other data, including SACT

6.2 Public Health England will collect the following outcomes through SACT unless it is determined by the SACT Operational Group that no meaningful data will be captured during the period of data collection:

- Number of patients starting treatment

- Baseline patient characteristics, including gender, age and performance status
- Treatment duration
- Overall survival

6.3 NHS England and NHS Improvement's Blueteq system will collect the following outcomes:

- Number of applications to start treatment

7 Data analysis plan

Clinical trials

7.1 The primary efficacy variables (co-primary endpoints) are the MRD negativity rate in peripheral blood at month 15 (MO 15) [VenO versus standard chemoimmunotherapy (SCIT)] and the interim PFS [VenIO versus SCIT].

The MRD co-primary endpoint will be analyzed as soon as all randomized patients have achieved the landmark 15 MO after randomization. Thus, final MRD analysis will take place as soon as the last patient randomized (LPI) has reached the time point MO 15 and all MRD samples have been analyzed. Giving an estimated 33 months recruitment period, time point of final MRD analysis was projected at month 49 in the trial protocol (v 5.1 of 15th February 2020).

A PFS interim analysis will be conducted after 65% of the total of 213 PFS events, i.e. 138 PFS events will trigger the interim analysis between standard chemoimmunotherapy and VenIO. PFS comparisons will not be performed for the other study arms at time of PFS interim analysis. PFS interim analysis is estimated to become available in [redacted] Please note that

this date may change as analysis will only be triggered when pre-specified number of events has been reached.

The final PFS analysis will be conducted once 213 PFS events occur (estimated time point = month 72) or approximately 73 months after first patient has been randomized. At this time point, PFS comparisons for other study arms, including the comparison of interest: standard chemoimmunotherapy and VenO, will be done according to a hierarchical test sequence to account for type I error control. Final PFS analysis is estimated to take place in January 2023. Please note that this date may change if the pre-specified number of events has not been reached. All patients will be followed until the final analysis at which point the clinical trial will end. After this long-term follow-up is planned in national and/or international registries.

7.2 [redacted]As mentioned above in 8.1 interim analysis is expected for the co-primary endpoints.

7.3 For the final PFS analysis data base lock is expected January 2023. The clinical study report is expected in Q4 2023.

Other data

7.4 At the end of the data collection period Public Health England will provide a final report for NHS England and NHS Improvement which provide analyses based on NHS England and NHS Improvement's Blueteq data and routinely collected population-wide data, including that collected via SACT. The necessary controls will be put in place to ensure that patient confidentiality is not put at risk. The report will be shared with the company in advance of the planned review of guidance. Where SACT is a secondary source of data,

availability of the final SACT report will be aligned to the availability of data from the primary source. The end of SACT data collection will be 8 months prior to the availability of the final SACT report to allow for NHS trusts to upload SACT data, data cleaning, and report production.

8 Ownership of the data

8.1 CLL13 is being run by the German CLL Study Group and the sponsor, the University of Cologne, owns the data.

8.2 AbbVie will be responsible for ensuring they have permission to share the clinical study report, including non-patient identifiable data and analysis as part of their submission for the guidance review.

8.3 The data analysed by Public Health England is derived from patient-level information collected by the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of Public Health England. Access to the data is facilitated by the Public Health England Office for Data Release. The company will not have access to the Public Health England patient data, but will receive de-personalised summary data, with appropriate governance controls in place.

8.4 The SACT dataset is a mandated dataset as part of the Health and Social Care Information Standards. All necessary governance arrangements through SACT, and other datasets brought together by Public Health England, have been established with NHS Trusts and NHS England and NHS Improvement.

8.5 Blueteq's Cancer Drugs Fund system data is owned by NHS England and NHS Improvement. NHS England and NHS Improvement is responsible for implementing Blueteq data collection and generally for the analysis of these data. NHS England and NHS Improvement, however, shares Blueteq data

with Public Health England for Cancer Drugs Fund evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and NHS Improvement and Public Health England.

9 Publication

9.1 Public Health England will produce a final report which includes analysis of data collected through SACT and from NHS England and NHS Improvement's Blueteq system. This report will be provided to NHS England and NHS Improvement and the company at the end of the managed access period. The final report will form part of NHS England and NHS Improvement's submission to the Cancer Drugs Fund guidance review, and will therefore be publicly available at the conclusion of guidance review.

9.2 Public Health England will produce interim reports, which will be shared with NHS England and NHS Improvement, NICE and the company at regular intervals during the data collection period. These reports will be used to determine whether real-world data collection is proceeding as anticipated, and will not form part of the guidance review.

9.3 Publications of any data from the Public Health England reports is not permitted until after the date of publication of the NICE committee papers (on the NICE website) following the first NICE guidance review committee meeting.

9.4 The contribution of all relevant individuals must be acknowledged in any publications regarding the data collection or analyses generated from the data collection arrangement. Authors will need to contact the NICE Managed Access Team for the full list of relevant individuals.

10 Data protection

10.1 The terms of clause 7 (data protection) of the managed access agreement, that apply between NHS England and NHS Improvement and AbbVie, shall also apply between the parties to this data collection arrangement in relation to the performance of their obligations under this data collection arrangement

11 Equality considerations

11.1 Do you think there are any equality issues raised in data collection?

☐ Yes ☒ No

Commercial Access Agreement

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The contents of this document have been redacted as they are confidential

- A glossary of terms relating to managed access agreements in the Cancer Drugs Fund is available here.